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Press release

The HOIL1 gene - the cause of a new rare disease

The researcher Capucine Picard, working with the team from Inserm unit 980 "Human genetics and infections diseases"/Université Paris Descartes under the leadership of Jean-Laurent Casanova, along with researchers from a CNRS/Institut Pasteur laboratory headed by Alain Israël have succeeded in identifying the part played by the HOIL1 gene in cases of paradoxal association of an immune deficiency with a chronic autoinflammatory deficiency and a muscular deficiency in 3 children from 2 different families. This study once more highlights the importance of genetics in the body's response to infectious agents. These works were published on line in the review Nature Immunology, of 28.10.12.

The science of genetics of infectious diseases arose from the observation that there is a wide variability of resistance to diseases from one person to another; that the same pathology could be fatal to one person, while benign or asymptomatic in others. The study also demonstrated that the predisposition to an infection is due to genetic particularities that result in variations in the molecular mechanisms of the immune response.

The 3 children, 2 of whom were monitored at the Hôpital Necker sick children's hospital, suffered simultaneously from 3 pathologies: invasive bacterial infections (pneumococcus or other), an autoinflammatory disease (inherited recurring fevers) and amylopectinosis (a muscular deficiency that can affect the cardiac muscles in particular). The fact that 2 siblings suffered from the same symptoms drew the researchers' attention to the hereditary genetic cause of this disease.

The team then carried out in-depth genetic studies in an attempt to identify the genetic defect responsible for these 3 observed pathologies: mutations of the HOIL1 gene.

Incomplete expression of this gene causes a dysfunction of the immune system. However, what makes this pathology unique is the fact that the genetic defect does not express in the same way, depending on the type of cells involved in the immune response. On the one had, this mutant gene is responsible for an over-reaction of leucocytes, which explains the autoinflammatory disease. On the other hand and quite to the contrary, this same genetic defect inhibits a response from other cells, which explains the susceptibility of these children to bacterial infections.

The HOIL1 molecule, derived from the gene of the same name, is responsible for an instability of the LUBAC complex that plays an important part in transmitting the signal received by the immune system cells in case of infection. This suggests that the genetic defect on HOIL1 in humans is responsible for a knock-on defect in the LUBAC complex, and that the LUBAC complex controls the immune response differently depending on the cell types involved.

Previously, the LUBAC complex had only been studied in mice. This is the first time that this deficiency has been detected in a human. For the moment, only 3 patients in France and in Italy have been identified with this HOIL-1 deficiency. The discovery of this new genetic defect may allow us to identify new patients in other regions of the world.

For further information

Source

Immunodeficiency, autoinflammation and amylopectinosis in humans with inherited HOIL-1 and LUBAC deficiency

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